REMARKS

Applicant's counsel thanks the Examiner for the careful consideration given the application. Claims 32-40, 43-45, 47-58 and 60-66 are pending. New claims 67-72 have been added. No new matter has been added.

Introductory Observations

Of the pending independent claims, claims 32 and 47 require that the measured autofluorescence is received from a skin tissue surface of at least 1 cm^2.

Claims 62 and 66 require that the measured autofluorescence is received from a skin tissue surface of at least 0.1 cm^2 and require that the autofluorescence is received only from a portion of the skin surface area that is irradiated with excitation radiation.

Claims 69 and 71 require that the measured autofluorescence is received from a skin tissue surface of at least 0.1 cm^2, that an advanced glycation/glycosylation end product content for a patient is or can be determined, that fluorescent radiation emitted in a direction at an angle to the direction of the excitation radiation is simultaneously received from different portions of the skin surface and that a measuring window for receiving the fluorescent radiation is oriented at an angle of 25-65° relative to the irradiated surface of the skin. Thus, the measurements are less disturbed by (variations in) mirror reflection, the received light is more evenly distributed over the skin surface area from which autofluorescence is received and the measurement window can easily be arranged so that it does not obstruct irradiation of the skin (p. 9, l. 4-28 of the application as filed).

Claims 70 and 72 require that the measured autofluorescence is received from a skin tissue surface of at least 0.1 cm^2, that an advanced glycation/glycosylation end product content for a patient is or can be determined and that a measuring window for receiving the fluorescent radiation is in a position spaced from the skin. The latter feature has the effect that the area of the skin from which the autofluorescence is received does not contact any light guiding solid material. The optical properties of such interface areas where the skin touches for instance a glass surface or a light guide are strongly influenced by several circumstances, such as humidity (sweat) and the exerted pressure. By avoiding such contact areas, disturbances of the measurement result by variations in optical properties caused by variations in circumstances as mentioned are avoided.

Moreover, by irradiating the skin via an open space (in which lenses and filters may be arranged), the efficiency of irradiating the skin is much higher than when the light is guided through a light guide and a wide variety of types of light sources can be used, since the light does not have to be coupled into a glass fiber light guide. This is particularly useful when determining an advanced glycation/glycosylation end product content for a patient.

The feature of irradiating via an opening in the support structure or in a surface contacting the skin is disclosed in the application as filed at p. 5, l. 9-13 and in claim 22.

Observations - 35 USC § 103

Kollias et al. in view of Carim et al.

According to the Examiner, starting off from Kollias et al., it would have been obvious to provide that the fluorescence is received from a skin surface area of at least 1 cm^2, because this is known from Carim et al.

Firstly, the combination of Kollias et al. and Carim et al. does not lead to a method or apparatus as claimed in any of the independent claims 32 and 47, because it is actually not disclosed in Carim et al. that the skin surface area from which radiation is received is at least 1 cm^2.

As is described in col. 17, l. 32-36 (see also Figs. 4 and 7B) of Carim et al., the radiation is received via a light guide 330 in contact with the skin surface of the finger. The optical fiber bundle 330 has a core diameter of about 1.2 cm (col. 17, l. 43-48). If the glass fiber light guide 330 would be massive, this would mean that the surface area of the skin in contact with the light guide 330 would be 1.13 cm^2.

However, of a fiber bundle end, not the entire cross-sectional area is available for receiving light. The net available cross section is related to the overall cross-sectional surface area by the "packing fraction" (see Carim et al. col. 15, l. 64-col. 16, l. 6). A common packing fraction of a fiber optic bundles is for instance 0.82. For a fiber optic bundle having a total cross-sectional area of 1.13 cm^2, that would result in a contacted skin surface area from which radiation may be received of $0.82 \times 1.13\ cm^2 = 0.93\ cm^2$.

Moreover, in Carim et al., none of the detectors (photodiodes 336) receives light from the entire skin surface area from which radiation is received. The light received in the fiber optic bundle is split into 6 to 10 channels 332, one for each wavelength of interest and the filtered light of each

channel shines on a respective one of the photodiodes 336 (Carim et al. col. 13, l. 47-50). Thus, each of the photodiodes receives radiation only from a fraction of the total skin surface area from which radiation is received. Thus, Carim et al. does not teach to lead light of a wavelength of interest received from a skin surface area of at least 1 cm^2 to a detector.

Furthermore, the fiber optic bundle 330 of Carim et al. is part of an example in the form of a transmission system. In such a system light is transmitted over a relatively large distance through body tissue, so that it is dispersed more widely than in reflectance measurement in which, on average, the light received from the skin has travelled through a very superficial portion of body tissue only. Although Carim et al. mentions the possibility of using optical reflectance techniques (col. 17, l. 27-31), it is not disclosed or even inherent that in a reflection measuring system a fiber optic bundle via which light is received would be arranged in the same manner as in the example based on transmission measurement.

Thus, the combination of Kollias et al. with Carim et al. does not lead to a method or an apparatus in which the radiation is received from a skin surface area of at least 1 cm^2.

Secondly, the skilled person would have had no reason to consider Carim et al. when looking for an improvement of the measurement of autofluorescence as disclosed by Kollias et al.

In Carim et al., absorption is measured so the measured light is a remainder of the light with which the tissue has been irradiated, while in Kollias et al. autofluorescence is measured, which is light at a different wavelength than the light with which the skin has been irradiated, which has been generated by the skin tissue itself and which is also subject to absorption. Accordingly, autofluorescence is roughly a factor 100 weaker than the intensity of light measured in absorption measurement. Autofluorescence is typically measured from a very superficial portion of the dermis only (cf. the preference of Kollias et al. for a short wavelength in view of its small penetration depth (col. 13, l. 42-43) and the preference for UV light as the excitation light (col. 9, l. 66)). In contrast, the examples disclosed by Carim et al. relate to transmission measurement, which is not suitable for autofluorescence measurement, because autofluorescence would not penetrate the body part to any significant amount and ultraviolet excitation radiation would be substantially extinguished before it reaches skin tissue at the side body part from which light is received, in particular taking into account the relatively short wavelength of excitation light used by Kollias et al.

Thirdly, it would not have been obvious to combine the teaching of Carim et al. with the measurement of autofluorescence as disclosed by Kollias et al.

As discussed above, Carim et al. relates to the measurement of optical properties of blood, whereas Kollias et al. relates to the measurement of autofluorescence of skin tissue. Skin tissue is located closely to the skin surface only, whereas the relative presence of blood decreases towards the skin surface. Accordingly, Carim et al. has an interest in taking measurements relatively deeply below the skin surface, whereas Kollias et al. is interested in the superficial layers of tissue only (cf. the preference of Kollias et al. for a short wavelength in view of its small penetration depth (col. 13, l. 42-43)).

Consistent with the interest in taking measurements from relatively deep below the skin surface, the only example described in detail by Carim et al. is measurement of transmission of light through a body part. In these measurements, the cross-section of the fiber optic bundle 326 via which light is introduced into the body part is smaller than the cross-section of the fiber optic bundle 330 via which light to be measured is received from the body part. This size of the fiber optic bundle 330 via which light to be measured is received from the body part appears to be related to the fact that in a transmission system light travels over a relatively large distance through the body tissue, so that it is dispersed quite widely. In a reflection system, such an effect does not occur, so the reason for choosing a larger cross-section for the receiving fiber optic bundle in a transmission system disclosed by Carim et al. is not applicable to a reflection system as disclosed by Kollias et al.

This is particularly noticeable from the contemplation in Kollias et al, that a short wavelength is advantageous in view of its small penetration depth (col. 13, l. 42-43) and the preference for UV light as the excitation light (col. 9, l. 66). With a small penetration depth and a fiber optic for receiving light next to a fiber optic via which excitation radiation is transmitted, increasing the cross-section of the fiber optic for receiving light would have little effect on the amount of light received, because the amount of light received from the skin would decrease rapidly with the distance to the irradiated skin surface portion.

Accordingly, the method or apparatus according to each of claims 32 and 47 would not have been obvious over Kollias et al. in view of Carim et al. Similar considerations apply to the dependent claims depending from any of claims 32 and 47 and to the dependent claims 67 and 68.

With respect to dependent claims 37 and 53 and independent claims 70 and 72, it is observed, that by irradiating the skin tissue via an opening in a surface contacting the skin and receiving the fluorescent radiation via a measuring window held at a distance from the skin, the skin is not contacted in the area from which the measurements are taken. The optical properties of such interface areas where the skin touches for instance a glass surface or a light guide are strongly influenced by several circumstances, such as humidity (sweat) and the exerted pressure. By avoiding such contact areas, disturbances of the measurement result by variations in optical properties caused by variations in circumstances as mentioned are avoided.

While Kollias et al. does mention the possibility of illuminating (not receiving autofluorescence) directly through the air (col. 14, l. 14-18), the only example described in detail provides for illumination via a fiber optic bundle contacting the skin. As this is also the illumination principle applied by Carim et al., combining Kollias et al. with Carim et al. would lead to a system where the light source and detector and skin are in direct contact with the skin, so this combination, if made at all, would lead away from the method and apparatus according to claims 37, 53, 70 and 72. Accordingly, it would not have been obvious to arrive at the method or instrument according to any one of the claims 37, 53, 70 and 72 on the basis of Kollias et al. in view of Carim et al..

The non-contact mode avoids the disadvantage of Kollias et al. that light has to travel at least the distance between the illumination fiber and the detection fiber through the tissue (see Fig. 10A), which may vary between illumination-detection fiber pairs, and may make the measurement more sensitive to variation in probe production and variations in scattering and absorption properties of the skin tissue.

In non-contact mode, the excitation light and the received autofluorescence have traveled under a large range of angles through the superficial dermis, including distances smaller than possible with a fiber probe as disclosed by Kollias et al.

Furthermore, the non-contact mode provides a simple solution for efficiently irradiating a large surface area and receiving autofluorescence from a large surface area. This offers the (patho)physiological advantage that the effects of minor skin irregularities (small hairs, small naevi) do not strongly affect the result and the advantage that a relatively strong signal can be obtained in a simple manner. The efficiency of the non-contact mode is illustrated by the contrast between, on the one hand, a 350 W Xe-arc lamp used by Kollias et al. (col. 6, l. 48) and

a 900 W lamp preferred by Carim et al. (col. 14, l. 4-7) and, on the other hand, a black light Hg-lamp with a power consumption of 8W in a prototype, and 4W in a current CE certified instrument according to claim 53.

The non-contact mode also allows performing a direct reflectance measurement with the same measurement set-up as the autofluorescence measurement.

With respect to claims 70 and 72, it is moreover observed that neither Kollias et al. nor Carim et al. discloses to generate, in response to the measured amount of fluorescent radiation, a signal which represents a determined advanced glycation/glycosylation end product content for the patient. Although Kollias et al. discloses that not the glucose, "...but a molecular component of the patient such as, for example, a component of skin or other tissue, that reflects or is sensitive to glucose concentration, such as tryptophan or collagen cross-links." is targeted, Kollias et al. teaches that the generated signal represents the current glucose level. Also this feature of claims 70 and 72 is not obvious over Kollias et al. combined with Carim et al.

With respect to dependent claims 36 and 51 and independent claims 69 and 71, it is observed, that by receiving fluorescent radiation emitted in a direction at an angle to the direction of the excitation radiation and holding the measuring window at an angle of 25-65° relative to the irradiated skin, the measurements are less disturbed by (variations in) mirror reflection and the received light is more evenly distributed over the skin surface area from which autofluorescence is received. Moreover, the measurement window can easily be arranged so that it does not obstruct irradiation of the skin (p. 9, l. 4-28 of the application as filed). Neither Kollias et al. nor Carim et al. discloses to hold the measuring window at an angle of 25-65° relative to the skin.

With respect to independent claims 62 and 66 and dependent claims 67 and 68, it is observed that neither Kollias et al. nor Carim et al. discloses to provide that the fluorescent radiation is received from a <u>portion</u> of the irradiated skin surface portion only. By receiving the fluorescent radiation from a portion of the irradiated skin surface portion only, the average distance through skin tissue over which excitation light and the fluorescence caused thereby and measured have travelled can be very short, so that relatively much autofluorescence can be generated at a moderate illumination intensity and the amount of autofluorescence is influenced to a relatively small extent by inter patient differences in absorption and scattering properties of the skin, such as differences in skin color.

<u>Anderson et al. in view of Carim et al. and general knowledge</u>

In the pending office action, it is stated that, claims 32, 34-37, 47, 49, 50, 56-58 and 66 are obvious over Anderson et al. in view of Carim et al.

From the reasons for rejection, it appears that only the rejection of claims 32, 34-37, 47 and 56-58 is based on combining Carim et al. with Anderson et al. while the rejection against claim 66 and the claims 49 and 50, which are dependent from claim 66, are based on Anderson et al. in combination with presumed general knowledge.

Anderson et al. discloses methods and systems for scanning a patient's skin, designating areas of affected skin, and selectively delivering high doses of phototherapeutic ultraviolet radiation to the designated areas (col. 2, l. 39-42). The disclosed spot size of the tracer beam at the patient's skin (which determines the size of the surface area from which autofluorescence can be simultaneously received) is: less than about 1 cm, and is typically about 1 to 4 mm. The skilled person would readily recognize that increasing the spot size would result in deteriorating the resolution of the scanning result and, accordingly, deteriorating the accuracy at which the skin areas affected by psoriasis and to be treated with the high doses of phototherapeutic ultraviolet radiation can be designated. Treating healthy skin with high doses of phototherapeutic ultraviolet radiation is clearly undesirable.

Therefore, increasing the spot size in the methods and systems according to Anderson et al. would be counterproductive to the very purpose thereof and would therefore not be obvious. Even if measuring from a larger skin surface would be known from Carim et al. (which it is not, as was explained above), such a teaching relating to the measurement of the hematocrite in blood would not constitute an incentive for the skilled person to increase the spot size in a method and system for scanning the skin and determining designated skin areas to be treated from the scanning result.

With respect to claims 36, 51, 69 and 71, it is observed that while it may indeed occur in Anderson et al. that the radiation is received from a skin surface portion at an oblique angle relative to the measurement window (the end front end of fiber 48), the fluorescent radiation is always received in a direction precisely opposite to the direction at which the excitation radiation has reached the area from which the fluorescent radiation is received. Accordingly, in Anderson et al., the received radiation has not been emitted in a direction at an angle to the direction of the excitation radiation.

It is noted that the illuminator 14 in Fig. 1 of Anderson et al. is only used for viewing and reflection measurement and not for generating the ultraviolet excitation radiation for causing the autofluorescence to be measured (see Anderson et al., col. 9, l. 34-38). Only the light source 34 (Fig 1) is for generating the scanning beam: the direction of the excitation radiation and the fluorescence to be detected being always in-line.

With respect to claims 66, 49 and 50: whether or not, in Anderson et al., the excitation radiation and the autofluorescence to be measured pass through the same optical fibers is irrelevant. Anderson et al. teaches that the measured light is received from a skin area coincident with the illuminated skin area. Whether the excitation radiation is passed through the same fibers as the measured fluorescence or not has no influence on this principle. Claim 66 requires that the measured fluorescent radiation is received from a portion of the irradiated skin surface portion only. Providing in Anderson et al. that the excitation radiation is passed through the same fibers as the measured fluorescence does not bring about this feature of claim 66.

With respect to claims 69-72, it is observed that neither Anderson et al. nor Carim et al. discloses generating a value representing a determined advanced glycation/glycosylation end product content for said patient in agreement with the measured amount of fluorescent radiation.

Kollias et al. in view of Anderson et al.

In response to the rejection of claims 62-65 in view of obviousness over Kollias et al. in view of Anderson et al., it is observed that the combination of Kollias et al. with Anderson et al. does not lead to a method according to claim 62.

As observed above, Anderson et al. discloses that the measured light is received from a skin area coincident with the illuminated skin area. Claim 62 requires that the measured fluorescent radiation is received from a portion of the irradiated skin surface portion only. Accordingly, combining Kollias et al. with Anderson et al. does not lead to a method according to claim 62 even if in Kollias et al. the same fiber optic bundle would be used for illuminating and for receiving the fluorescent radiation.

Moreover, it would not have been obvious to consider Anderson et al. when looking for an improvement of what is disclosed by Kollias et al. Kollias et al. disclosed a method and apparatus for detecting autofluorescence as an indicator for the blood glucose level, which

constitutes an aspect of the general condition of the patient, whereas Anderson et al. discloses methods and systems for scanning a patient's skin, to distinguish designated areas of affected skin from healthy skin, and to selectively deliver high doses of phototherapeutic ultraviolet radiation to the designated areas (Anderson et al., col. 2, l. 39-42), i.e. a solution for distinguishing affected skin areas to be treated from skin areas not to be treated. A measurement technique for measuring an aspect of the general condition of a patient should preferably depend as little as possible from the location where of the skin from which the measurement is taken. Accordingly, it would not have been obvious to consider Anderson et al., a document specifically relating to identifying and designating affected skin areas from not affected skin areas, when looking for improvement of a preferably location independent measurement technique.

Although the rejection based on Kollias et al. in view of Anderson et al. was not applied against claim 66, it is observed that the arguments in support of claim 62 are equally applicable to claim 66.

For all the foregoing reasons, it is believed that all of the claims now present in this application are in condition for allowance, which is respectfully requested. If any further fees are required by this communication, please charge such fees to our Deposit Account No. 16-0820, Order No. VOB-34537US1.

Respectfully submitted,
PEARNE & GORDON LLP

By John P. Murtaugh
John P. Murtaugh, Reg. No. 34226

1801 East 9th Street, Suite 1200
Cleveland, Ohio 44114-3108
Phone: (216) 579-1700
Fax: (216) 579-6073

Date: September 9, 2008